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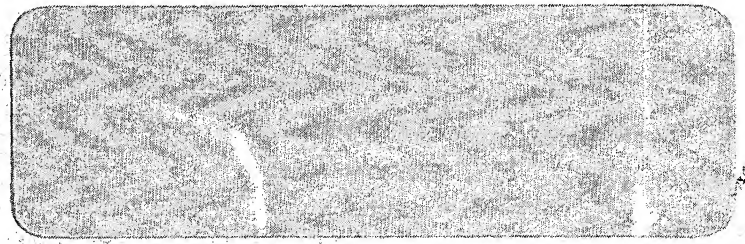

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,551	12/11/2001	Keith D. Allen	R-227	4290

7590 03/25/2004

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,551	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 12/22/03 has been entered.

New claims 33-46 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

New claims 33-46 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is **specific and substantial,** or a well established utility, partially for the reasons already set forth in the previous Office Action mailed on 6/17/2003 (pages 3-5) and for the following new ground of rejection necessitated by Applicants' amendment.

The invention is drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a transgenic mouse whose genome comprises a disruption (both homozygous and heterozygous disruption) in the BSMAP gene as well as a cell or tissue obtained from the same transgenic mouse, a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

The specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, wherein the transgenic mouse displays **supposedly a significantly increased Prepulsed inhibition**, particularly with a 100 dB prepulse in comparison with the age- and gender matched wild-type control mouse (page 51, lines 29-31). However, upon examination of Figure 3, the only relevant data provided by the instant specification, the observed difference in Prepulsed inhibition between the transgenic mouse comprising a homozygous disruption of the BSMAP gene and the wild-type control mouse is apparently not statistically significant (please note that the error bars of the Prepulse inhibition values for the control wild-type mouse extend to and include the mean Prepulse inhibition values for the transgenic knockout mouse). Therefore, there is no apparent significant difference or obvious difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption of the BSMAP gene. It is noted that the Prepulse inhibition (PPI) test only reflects one component of the startle reflex response. Moreover, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2), all of which clearly indicate that the homozygous mutant mouse of the instant invention appears to be not an acceptable model of schizophrenia. Furthermore, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including

schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002), and that even in 2002 there is still no gene or genes that have been confirmed as "schizophrenia genes". Therefore, how can any agent modulating a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of schizophrenia?

At the effective filing date of the present application, little was known about the physiological role or function of the BSMAP gene. Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). Because the defined function for the BSMAP or its gene is not known and is not taught in the specification, the invention has no utility which is **specific** and **substantial** at the effective filing date of the present application. The speculation that BSMAP may play a generic role in brain function or its gene disruption is somehow associated with schizophrenia is not deemed to be a specific and substantial utility for the presently claimed invention.

The specification asserts a variety of utilities for the claimed invention, including uses of the cell-and animal-based systems of the present invention as models for diseases, for identifying compounds that ameliorate disease symptoms, for production

of antibodies, for identifying agents that modulate the expression or the function of the BSMAP gene. However, such uses would require the determination of the physiological function or role of the BSMAP gene and its gene product, and in the absence of such guidance provided by the instant specification and in the prior art, they do not constitute a substantial utility at the effective filing date of the present application. A substantial utility is a utility that defines a "real world" use. Utilities which require further research to identify or confirm a real world use are not substantial utilities.

For the reasons set forth above, a skilled artisan would not be able to use the presently claimed invention for any substantial purpose without further research and experimentation.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed 12/22/03 (pages 5-6) have been fully considered, but they are not found persuasive.

Applicant asserts that Applicant clearly disclosed in the instant application that a statistically significant difference was observed between the transgenic mouse and wild type mice. Applicant further argues that the presence of overlapping error bars does not necessarily establish or support a lack of statistical significance as asserted by Examiner. Applicant also argues that with respect to the new set of claims, prepulse inhibition, at the time of filing, was known in the art and taught by the instant specification to be associated with schizophrenia. Therefore, the transgenic mouse as claimed would be supported by a variety of utilities, such as, for example, the

investigation into and/or discovery of therapeutic agents related to schizophrenia or as an animal model related to schizophrenia.

Firstly, common sense would dictate that there is no apparent statistically significant difference between the PPI values observed after a 100 decibel prepulse for the homozygous mutant mouse and a wild-type mouse in Figure 3. The range of PPI values for both the homozygous mutant mouse and a wild-type mouse is overlapped as shown in Figure 3. This factual evidence is opposite to Applicant's assertion that there is a statistically significant difference in PPI responses observed between the transgenic mouse and wild type mice. Therefore, on the basis of the data presented in this application, it is reasonable to conclude that there is no significant difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption of the BSMAP gene.

Secondly, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002). Additionally, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2). Moreover, there is still no gene or genes that have been confirmed as "schizophrenia genes" in 2002, let alone at the effective filing date of the present application (Geyer et al., Mol. Psychiatry 7:1039-

1053, 2002). Furthermore, nothing was known about the physiological role or function of the BSMAP gene, and that Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) also state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19" (page 55, col. 2, second last sentence) in reference to the location of human BSMAP on human chromosome 19p12. Thus, at the effective filing date of the present application it is not clear what is the significance of the data reported in Figure 3, and that the homozygous transgenic mouse of the present invention has anything to do with schizophrenia.

Accordingly, the speculation that BSMAP may play a generic role in brain function or its gene disruption is somehow associated with schizophrenia is not deemed to be a specific and substantial utility for the presently claimed invention. Therefore, new claims 33-46 are rejected under 35 U.S.C. 101 for the reasons set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 33-46 are rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35 U.S.C. 101, one skilled in the art would not know how to use the claimed invention at the effective filing date of the present application.

The specification is not enabled for the present claimed invention in part for the same reasons already set forth in the previous Office Action mailed on 6/17/03 (pages 6-10), and for the following reasons directly to the new claims.

(1) The breadth of the claims. The instant claims are drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a transgenic mouse whose genome comprises a disruption (both homozygous and heterozygous disruption) in the BSMAP gene as well as a cell or tissue obtained from the same transgenic mouse, a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). In effect, little was known about the physiological role or function for BSMAP gene and its gene product. Additionally, even several years after the effective filing date of the present application (12/13/2000), there is still no gene or genes that have been confirmed as "schizophrenia

genes". Furthermore, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002).

(3) The amount of direction or guidance provided. Apart from the disclosure of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting an increased Prepulsed inhibition with a 100 dB prepulse that is not statistically significant (see Figure 3) in comparison with the age- and gender matched wild-type control mouse, the specification fails to provide sufficient guidance for a skilled artisan on how to use such homozygous mutant mice. On the basis of the instant disclosure, it is not clear what is the significance of the non-statistical difference in the PPI responses observed for the homozygous mutant mouse and a wild type mouse. It is noted that the Prepulse inhibition test only reflects one component of the startle reflex, and it is not a representative test for evaluating stimulus processing abnormality in general. While it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002). Additionally, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2). Moreover, there is still no gene

or genes that have been confirmed as "schizophrenia genes" in 2002, let alone at the effective filing date of the present application; and that nothing was known about the physiological role or function of the BSMAP gene or any genetic disease has been mapped to locus of the BSMAP gene (Elson et al.; Biochem. Biophys. Res. Commun. 264:55-62, 1999). Therefore, how can any agent modulating a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of schizophrenia?

It is also unclear on the basis of the present disclosure, how can one **use** a transgenic mouse comprising a heterologous disruption of the BSMAP gene without any phenotype distinguishable from a wild-type mouse? Similarly, it is unclear how cells obtained from any transgenic mouse of the presently claimed invention that do not possess any phenotype can be used and for what purposes. As enablement requires the specification to teach how to make and **use** the claimed invention, given the lack of sufficient guidance provided by the present application and in light of the state of the relevant prior art as discussed above, it would have required undue experimentation for a skilled artisan to make and **use** the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed 12/22/03 (pages 7-8) have been fully considered, but they are not found persuasive.

Applicant relies on the same arguments in response to the utility rejection under 35 U.S.C. 101 for overcoming the rejection under 35 U.S.C. 112, First Paragraph. With

respect to the new set of claims, Applicant asserts that one skilled in the art would be able to make and use the presently claimed invention.

Applicant's arguments in response to the utility rejection are not found persuasive for the reasons already set forth in the above Response to Arguments. Additionally, Examiner maintains that based on the analysis of the Wands factors already discussed at length above, an ordinary skilled artisan would still not know how **to use** the presently claimed invention.

Therefore, new claims 33-46 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

Claim 46 is indefinite because there is no connection between the step of determining whether the potential therapeutic agent modulates prepulse inhibition in the transgenic mouse with modulation of seizure susceptibility. Is there a separate step for determining seizure susceptibility? As written, the metes and bounds of the claim are not clearly determined.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/015,551	Applicant(s)/Patent Under Reexamination ALLEN, KEITH D.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	D	US-			
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Geyer et al. Mouse genetic models for prepulse inhibition: an early review. Mol. Psychiatry 7:1039-1053, 2002.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Molecular Psychiatry (2002) 7, 1039–1053

www.nature.com/mp

REVIEW

Mouse genetic models for prepulse inhibition: an early review

MA Geyer[1], KL McIlwain[2,4] and R Paylor[2,3]

[1]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA; [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; [3]Division of Neuroscience, Baylor College of Medicine, Houston, TX, USA

Prepulse inhibition (PPI) is the phenomenon in which a weak prepulse stimulus attenuates the response to a subsequent startling stimulus. Patients with schizophrenia and some other neuropsychiatric disorders have impaired PPI. Impaired PPI in these patient populations is thought to reflect dysfunctional sensorimotor gating mechanisms. Recently, various inbred mouse strains and genetically modified mouse lines have been examined to investigate the potential genetic basis of sensorimotor gating. This review provides a synopsis of the use of mouse models to explore genetic and neurochemical influences on PPI. Studies describing the PPI responses of various inbred strains of mice, mice with genetic mutations, and mice treated with various drugs prior to July 2001 are reviewed. The continuous nature of the distribution of PPI responses among inbred strains of mice indicates that PPI is a polygenic trait. Findings from spontaneous and gene-targeted mutants suggest that mutant mice are important tools for dissecting and studying the role of single genes and their products, and chromosomal regions in regulating PPI. Pharmacological studies of PPI have typically confirmed effects in mice that are similar to those reported previously in rats, with some important exceptions. The use of mice to study PPI is increasing at a dramatic rate and is helping to increase our understanding of the biological basis for sensorimotor gating.
Molecular Psychiatry (2002) **7**, 1039–1053. doi:10.1038/sj.mp.4001159

Keywords: prepulse inhibition; knockout mice; transgenic mice; startle; schizophrenia

Introduction

The startle response is defined as an unconditioned reflexive response to a sudden environmental stimulus. Plasticity of the startle response is evident in paradigms such as prepulse inhibition (PPI) and habituation. PPI is the phenomenon in which a weak prestimulus or prepulse suppresses the response to a subsequent startling stimulus.[1,2] As reviewed elsewhere,[3] many studies have shown that patients with schizophrenia[4] and schizotypal personality disorder[5] have impaired PPI. The PPI impairment observed in schizophrenia patients is thought to reflect an underlying problem with inhibitory mechanisms in neuronal circuitry used for sensorimotor gating.[6] Abnormal PPI has also been observed in other neuropsychiatric populations including obsessive-compulsive disorder[7] and Huntington's disease.[8] For more details regarding the human studies of prepulse inhibition the reader is referred to a recent review by Braff *et al*.[3] PPI is highly conserved among vertebrates, and is one of the few paradigms in which humans and rodents are tested in similar fashions. Thus, PPI has quickly become the test of choice for scientists developing rodent models to study sensorimotor gating deficits.[3,9,10]

Until recently, the rat has been the predominant species used for studying the neurobiology of PPI. Although key neuroanatomical and neuropharmacological influences on PPI have been identified using rats,[9,10] the mouse has quickly gained in popularity for studying the genetic basis of sensorimotor gating using the PPI paradigm. Here we review the findings from three major areas of research that utilize mouse genetic models to begin to identify and understand the genes that regulate PPI. First, findings from studies using various inbred strains of mice have been critical to establish that PPI is a polygenic trait, that various background strains may be more useful for targeted and random mutagenesis studies of PPI, and that differences in basal sensory function are important determinants of the PPI response. Second, we describe the mutant strains that have been used to study the roles of genes that regulate PPI. Third, the pharmacology of PPI in mice is presented and we conclude with a brief discussion of the future directions.

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Received 9 January 2002; revised 6 March 2002; accepted 15 March 2002

Inbred strain studies

Willott *et al*[11] published the first report describing differences in PPI among inbred strains of mice. There were at least three important findings from this initial paper. First, mice could be used to study the PPI response. Second, parameters could be used to show a relationship between known hearing abnormalities and levels of PPI (see discussion below regarding this issue). Third, the differences in PPI between strains suggests that it may be possible to use mice to study the genetic basis of PPI. A recent book '*Handbook of Mouse Auditory Research. From Behavior to Molecular Biology*' edited by Willott[12] is an excellent resource for the interested reader in topics such as audiology,[13] the peripheral[14] and central auditory systems,[15] hearing loss in mice,[16] and other characteristics of the startle response.[17]

Recently, three independent papers were published that confirmed and extended the observation that large differences exist in levels of PPI among inbred strains of mice. Bullock *et al*[18] evaluated the PPI responses of eight inbred strains of mice, Logue *et al*[19] evaluated 13 inbred strains and seven F1 hybrids for PPI, and Paylor and Crawley[20] tested PPI in 13 inbred strains of mice. Although there are subtle differences in the results between these studies, there are some very remarkable similarities. Each study clearly showed that the acoustic startle response and PPI are continuously distributed traits among inbred strains of mice. This observation is important because it confirms the earlier finding by Willott,[11] that PPI is a polygenic trait. Because the trait is polygenic, quantitative trait loci mapping strategies have been initiated in an attempt to identify chromosomal regions that influence the PPI response. Hitzemann *et al*[21] recently provided the first set of data indicating that QTL mapping strategies may indeed provide insight into the genetic basis of PPI using mice. Briefly, Hitzemann and colleagues[21] found significant QTLs using the combined analyses of BXD (ie C57BL/6 × DBA/2) recombinant inbred lines and from BXD F2 intercross for PPI on mouse chromosome 5 and 11. Other investigators are also performing QTL analyses using different inbred lines of mice which will provide interesting data when combined with the findings from Hitzemann *et al*;[21] however, these studies are still in progress and the findings have not been published.

Another important finding that was common among the three studies is that overall levels of PPI are not correlated with the baseline startle response.[20] This latter observation indicates that startle reactivity and PPI are dissociated, which has been found in a wide variety of studies using rats.[9,10] Finally, the strain distribution patterns for PPI from these studies may have implications for other genetic studies using mutant mice. For example, if an investigator is planning to generate a mouse with a specific targeted mutation or a transgenic insertion, it may be important to consider the genetic background on which the mutation is to be engineered.[22]

The findings by Willott *et al*[11] highlight the concern regarding the influence or confound of hearing impairments when assessing levels of PPI. Willott and colleagues have shown with several inbred mouse lines that there can be a relationship between levels of PPI and hearing impairments. There are several strains of mice that develop high frequency hearing loss as they mature (ie DBA/2 and C57BL/6). Therefore, the major concern regarding the influence of hearing impairments on PPI is most relevant when pure tones or high frequency stimuli are used. Hence, one must be cautious when choosing the type of auditory stimuli for PPI studies. Importantly, each of the three studies listed above used broad-band white noise as the acoustic stimuli, and studied mice that were 'young' (ie 2–3 months of age). Therefore, their findings are less likely to influenced by basal differences in hearing.

Lastly, studies with inbred strains of mice have shown that there are developmental changes in levels of PPI. Some strains of mice—such as C57BL/6—demonstrate a dramatic and abrupt increase in levels of PPI as the mice mature.[23] This increase in PPI appears to be related at least in part to developmental changes in high-frequency hearing loss. Therefore, the age of a test subject is another important consideration when using mice to study the genetics and/or neurobiology of PPI.

Mutants

The molecular techniques to generate mice with specific targeted mutations have provided scientists with the tools to dissect and understand the roles of genes and their products involved in central nervous system (CNS) function. A detailed description of how mutant mice are generated is beyond the scope of this review. The interested reader is referred to one of the several papers, chapters, or books describing the molecular techniques used to generate mutant mice.[24]

Four types of mutant mice have been used in PPI studies—mice carrying deletions of single genes, deletions of whole chromosomal regions, genetic insertions, and those with spontaneous mutations. Most of the mutant mice used in PPI studies are standard knockout mutations in which a single gene has been altered using homologous recombination leading to the absence of the protein product made by that gene. The PPI response of several spontaneous mutant lines has also been evaluated. Mice with transgenic insertions of human genes have also been studied. Finally, mutant mice with chromosomal deletions, which include multiple genes, have been generated and tested for levels of PPI. The various types of mutant mice have been used in studies of PPI for several reasons, including testing hypotheses about specific receptor proteins, modeling human genetic disorders, and identifying new candidate genes regulating sensorimotor gating. The following sections describe the various lines of mutant mice that have been used in studies with PPI. The findings obtained from these experiments clearly demonstrate that mutant mice can be a powerful tool

to study the role of genes and other cellular signaling events in sensorimotor gating.

Hypothesis testing
Several lines of knockout mutant mice have been used to test specific hypotheses about the role of particular neurotransmitter receptor proteins in PPI. In several of the studies using receptor-specific deficient mutant mice, the effects of different drugs on PPI have also been evaluated. The findings from these studies have provided critical information about the role of specific receptors in regulating basal PPI in addition to the role of receptor subunits in regulating the effects of different drugs on PPI.

Serotonin receptors Pharmacological evidence from two different 5-HT receptor deficient mice have been generated and used to test the hypothesis that serotonergic receptor-mediated processes regulate sensorimotor gating. Dulawa, Geyer, and colleagues[25] reported that 5-HT1B-deficient mice exhibit small increases in PPI, that were significant with prepulse intensities that were 4 dB above background in females. Two other papers by the Geyer laboratory also reported small increases in 5-HT1B-deficient mice that were not statistically reliable. Although they are not large effects, it appears that the majority of data indicate that female 5-HT1B-deficient mice have slightly increased PPI. It is interesting to note that the increase in PPI reported for the 5-HT1B-deficient mice appears to be gender dependent. Both Dulawa[25] and Dirks[26] have shown that male 5-HT1B-deficient mice have normal levels of PPI. The fact that 5-HT1B-deficient mice have increased PPI suggests that activation of this serotonin receptor subtype acts to decrease the processes underlying the PPI response.

The Geyer laboratory has also studied the PPI response in mice deficient in 5-HT1A receptors.[27,28] In contrast to the slight, but significant increase in PPI seen in female 5-HT1B-deficient mice, the PPI response is normal in female[27] and male[26] 5-HT1A-deficient mice. This negative result does not mean that 5-HT1A receptors are not involved in PPI. As discussed below, the data from pharmacological studies support a role for the 5-HT1A receptors in regulating PPI.

Data from knockout mice and pharmacology in normal mice (see below) support the hypothesis that 5-HT receptors regulate the PPI response. Further support for this hypothesis comes from experiments that combine the use of drugs that act at 5-HT1A and 5-HT1B sites and mice that are deficient in the 5-HT1B receptors. In a study by Dulawa *et al*,[27] wild-type 5-HT1A and 5-HT1B-deficient mice were given either saline, the 5-HT1A/1B agonist RU24969, or the 5-HT1A agonist 8-OH-DPAT. In addition, the effects of the 5-HT1B agonist anpirtoline on PPI was tested in wild-type and 5-HT1B-deficient mice. The effect of anpirtoline on PPI in the 5-HT1A-deficient mice was not tested. The results from these experiments showed that RU24969 impaired PPI in wild-type and 5-HT1A-deficient mice, but had no effect on 5-HT1B-deficient mice. 8-OH-DPAT increased PPI in wild-type mice (also see below) and 5-HT1B-deficient mice, but had no effect on 5-HT1A-deficient mice. Anpirtoline impaired PPI in wild-type mice, but had no effect on 5-HT1B-deficient mice. Finally, in a separate study, Dulawa *et al*[29] showed that both MDMA and MBDB, which are serotonin releasing agents, increased PPI in 5-HT1B-deficient but not wild-type mice. Taken together, the data from the 5-HT1A- and 5-HT1B-deficient mice, plus the effects of different drugs in these mutant lines, suggest that 5-HT1B receptor activation leads to a reduction in the PPI response and activation of 5-HT1A receptors increases PPI in mice.[25,27–29]

Dopamine receptors Overactivity of the dopaminergic system has been hypothesized to contribute to aspects of schizophrenia. In rodent models, dopamine has been shown to regulate sensorimotor gating.[30,31] Pharmacological studies in rats (reviewed in Ref 9) and mice (see below) indicate that the D2 receptor family (ie D2, D3, and D4 subtypes) appears to play a key role in mediating the effect of dopamine on PPI. In rats, much of the evidence for this conclusion derived from studies showing that D2-family dopamine antagonists block the effects of dopamine agonists on PPI. However, the pharmacological tools available were not sufficiently selective to determine which of the D2 family of receptors was most critical in this regard. The availability of knockout mice for the D2, D3, and D4 receptor subtypes enabled a more definitive test of the hypothesis that the D2 subtype was specifically involved. Thus, Ralph, Geyer, and colleagues[32] tested the effects of the dopamine releaser amphetamine, which should indirectly activate all dopamine receptors, on PPI in knockout mice for each of these receptor subtypes. Amphetamine was effective in disrupting PPI in all three wild-type lines and in both D3 and D4 knockout mice. In contrast, amphetamine had no effect on PPI in the mice lacking only the D2 receptor subtype, confirming the hypothesis. Further support for this conclusion comes from preliminary evidence indicating that the effects of amphetamine on PPI are normal in D1 knockout mice (Geyer, Ralph, and Low, unpublished observations). The role for dopamine and the D2 receptor in PPI has recently received additional support using mutant mice that are deficient in the dopamine transporter (DAT). Ralph *et al*[33] found that DAT-deficient mice have impaired PPI. In addition, they showed that the D2-family antagonist raclopride increased PPI in DAT-deficient mice while having no effect in wild-type mice. In contrast, the D1-family antagonist SCH23390 did not alter the PPI response in DAT-deficient mice. These findings confirm and extend the rat pharmacological studies supporting a role for the D2, but not D1 receptor in regulating sensorimotor gating.

Adrenergic receptors There are three subtypes of the alpha2-adrenoreceptors that are encoded by three genes. These receptors mediate many of the effects of norepinephrine (NE) in the CNS. In addition, these

receptors can regulate the release of NE, 5-HT, and DA. The alpha 2c subtype is expressed primarily in the CNS, and is particularly high in striatum and hippocampus.[34] The alpha2-adrenoreceptors have modulatory roles in several neuropsychiatric disorders including schizophrenia and depression.[35–37] To determine if alpha2c-adrenoreceptors regulate processes underlying sensorimotor gating, Sallinen *et al*[38] evaluated PPI levels in alpha2c-deficient mice. In addition, PPI levels in mice with tissue-specific overexpression of the alpha2c subtype were examined. The results from these experiments clearly showed that the alpha2c-deficient mice had impaired PPI, while mice overexpressing the alpha2c subtype had significantly higher levels of PPI. These findings implicate a role for the alpha2c subtype in sensorimotor gating. In addition, Sallinen *et al*[38] showed that drugs that act in a nonselective manner at the alpha2 site attenuate the increased PPI response in the alpha2c-overexpressing mice. Taken together, the results from the alpha2c knockout and overexpressing mice and the pharmacological treatment of the overexpressing mice support a role for the alpha 2c-adrenoreceptor in regulating sensorimotor gating. There are two caveats to this study that one should keep in mind. First, the alpha2c mutant mice also have alterations in dopamine and serotonin metabolism. Therefore, some of the effects on PPI could be related to these changes.[38] Second, in their first experiment, the alpha2c-deficient mice showed impaired PPI. However, in subsequent studies the alpha 2c-deficient mice that received a drug vehicle injection did not show impaired PPI. Therefore, it is not clear if the impaired PPI seen in alpha2c-deficient mice is a reliable effect. It is clear that the alpha2c-overexpressing mice routinely have increased PPI because it was seen in all the experiments presented in the paper by Sallinen *et al*.[38]

Nicotine receptors There are several lines of evidence that are suggestive of a role for the alpha7 nicotinic acetylcholine receptor (nAChR) subtype in sensorimotor gating. First, in the auditory event-related-potential paradigm that assesses sensory rather than sensorimotor gating nicotine increases sensory gating, in both animals and humans.[39–46] There is some evidence for similar nicotine effects in the PPI model of sensorimotor gating.[40,41,45] Second, intraventricular injections of alpha-bungarotoxin (alpha-BTX), which binds with high affinity to the alpha7 nAChR, disrupt hippocampal sensory gating.[47] Third, there is a significant correlation between levels of sensory gating of auditory-evoked potentials and alpha-BTX binding in the hippocampus among inbred strains of mice.[48] Similarly, there is a correlation between levels of PPI and alpha-BTX.[18] Finally, Freedman *et al*[49] showed that sensory gating differences associated with schizophrenia[6,50,51] show linkage to human chromosome 15 in a region near the alpha7 locus. Taken together, these and related findings provided evidence for the hypothesis that there is a relationship between sensory and perhaps sensorimotor gating and the alpha7 nAChR.

Paylor *et al*[52] used alpha 7-nAChR-deficient mice to test the hypothesis that alpha7 nAChR are required for normal PPI. The alpha-7 nAChR mutant mice were created using standard homologous recombination strategies.[53] In contrast to the *a priori* predictions based primarily on the auditory sensory gating paradigm, the findings from this study did not support the hypothesis with respect to sensorimotor gating as measured by PPI. Indeed, alpha7-deficient mice displayed similar levels of PPI as their wild-type littermates.[52] These findings are important because: (1) they suggest that an animal does not need alpha7 nAChR to show normal PPI; and (2) they demonstrate the utility of knockout mice for testing specific hypotheses. It is also interesting to note that Olivier *et al*[54] recently found that antipsychotic drugs such as clozapine increase PPI in mice, but drugs that are alpha7-nAChR agonists produced no significant increase in PPI in mice. These pharmacological findings support the data from the knockout mice which suggest that alpha7 nAChR may not regulate PPI. Research is currently underway to continue to test the hypothesis by crossing the alpha7 nAChR-deficient mice into multiple genetic backgrounds. These findings also raise the important point that sensory gating, as measured by the event-related potential paradigm, and sensorimotor gating, as measured by PPI of startle, may not be redundant measures of the same process, as discussed elsewhere.[55] Indeed, recent studies in schizotypal patients indicate that most patients have deficits in either sensory gating or sensorimotor gating, but not in both measures.[56] Hence, it will be critical to assess sensory gating measures in the alpha7 nAChR-deficient mice.

Hippocampal and cortical development

A key feature of several neuropsychiatric disorders including schizophrenia is a pathology of limbic and prefrontal brain regions.[57–60] Although the developmental time period when this pathology emerges remains unclear, some data support the hypothesis that some of the brain pathology occurs during early brain development.[61–63]

Findings from animal models suggest that ventral hippocampal-formation damage in rats in early life impairs brain function leading to several behavioral abnormalities including impaired PPI.[63] Damage to the same brain region during adulthood does not impair basal PPI,[64,65] but such adult lesions do appear to increase the sensitivity to the PPI-disruptive effects of apomorphine.[65] Together, these findings suggest that normal development of brain regions such as the hippocampus might be essential for normal sensorimotor gating. There are several single gene mutations in mice that lead to abnormal brain development,[66] however, this review focuses on those mutations that lead to: (a) abnormal hippocampal development and (b) that have been tested for sensorimotor gating.

Reelin and Reeler mutants Reelin is a large extracellular protein involved in neuronal migration. Reeler mutant mice, which were derived from a spontaneous

mutation, have abnormal neuronal migration leading to several topographical abnormalities in cortical regions, in the hippocampus and in hippocampal connections.[67] In addition, there is degeneration of cerebellar Purkinje cells in Reeler mutant mice during adulthood.[68] Recent reports have shown that levels of reelin mRNA and protein are decreased in several brain regions including prefrontal cortex, hippocampus, and cerebellum from schizophrenia patients.[69] These findings indicate that down-regulation of reelin—together with glutamic acid decarboxylase 67 (GAD67)—may contribute to the types of brain dysfunction that lead to the expression of certain neuropsychiatric conditions.[70]

Reeler mutant mice have been used to test the hypothesis that decreased levels of reelin result in abnormal behavioral responses in mice that may be related to behavioral abnormalities observed in schizophrenia patients. Tueting *et al*[71] found that heterozygous Reeler mutant mice have an age-related decrease in PPI compared to wild-type controls.[71] These intriguing findings are consistent with the hypothesis that levels of reelin may regulate sensorimotor gating. That Reeler mutant mice have impaired PPI is also consistent with the notion that abnormal brain development results in impaired sensorimotor gating. Then again, it is difficult to know if the impaired PPI in Reeler mutant mice is related to having low levels of reelin at the time of testing, and/or the result of abnormal brain development. The answer to this question will await studies using inducible mutant mice.

Neural cell adhesion molecule Barbeau *et al*[72] reported a decreased expression of neural cell adhesion molecule (N-CAM) in brains of individuals with schizophrenia. N-CAM is an abundant cell surface receptor that is widely expressed in the CNS and plays a critical role in cell migration during CNS development. Although the olfactory bulb is the most notably disorganized brain structure in N-CAM-180 knockout mice, the hippocampus is also affected. The pyramidal cell layer of CA3 appears to be somewhat bifurcated and the cells are more dispersed in N-CAM-180 deficient mice.[73] Given the suggested relationship between N-CAM expression and schizophrenia and a role for N-CAM in brain development, the PPI response in N-CAM deficient mice was studied. Wood *et al*[74] showed that the levels of PPI of N-CAM-deficient mice were significantly lower than the control CF-1 inbred mice. Although it is not clear what brain abnormality might underlie the PPI impairment, the findings are intriguing and suggest that the type of developmental abnormalities associated with N-CAM deficiency result in impaired sensorimotor gating. Unfortunately, in the study by Wood *et al*,[74] the responses of N-CAM knockout mice were compared to CF-1 inbred mice and it is unclear how many generations the N-CAM mutant mice had been backcrossed prior to testing. Hence, some of the observed differences in PPI may be due to differences in genetic background.[20]

Lis1 The findings from two other mutants described below, however, suggest that abnormal brain development and abnormal hippocampal development in particular, does not always lead to impaired PPI. Recently, the Paylor laboratory[75,76] had the opportunity to study the behavioral responses of two different mutant mice that have abnormal hippocampal development. Humans with hemizygous deletions of 17p13.3 have isolated lissencephaly sequence or Miller–Dieker syndrome. These disorders result from abnormal neuronal migration that causes the brain to develop with smooth surfaces (ie lissencephaly). Individuals with lissencephaly have profound mental retardation and other neurological abnormalities. The gene[77] for type 1 lissencephaly, LIS1, is a platelet-activating factor acetylhydrolase (PAFAH, isoform 1b). The expression pattern of murine Lis1 is consistent with its role in neuronal migration and development. To better understand the role of Lis1 in neuronal migration and brain development, Lis1 1 mutant mice were created using standard homologous recombination.[78] Lis1 heterozygous mutant mice have disorganized cortical and hippocampal brain regions. The behavioral responses of Lis1 heterozygous mutant mice were characterized on a behavioral test battery that included assays for learning and memory and PPI.[75] As expected, the results from these studies showed that the Lis1 mutant mice had abnormal learning performance. In addition, the Lis1 mutant mice have some ataxia and motor coordination impairments. However, their levels of PPI were not significantly different from the littermate controls. These findings suggest the type of abnormal brain development that is associated with Lis1-related neuronal migration defects does not lead to abnormal sensorimotor gating and that the expression of normal PPI does not require the abnormal brain development

Lhx5 Lhx5 is a member of the LIM homeobox gene family that regulates development of the nervous system.[79] Lhx5 is a gene that appears to be essential for normal hippocampal development. Adult mice generated with a Lhx5 mutation have absent or disorganized hippocampal neuroanatomy,[80] yet remaining portions of the brain appear to be quite normal. To better understand the functional consequences of abnormal hippocampal development, Lhx5 mutant mice were evaluated on a battery of behavioral tests.[76] Not surprisingly, Lhx5 mice had severe learning and memory impairments and exhibited some ataxia and motor coordination impairments. However, somewhat to our surprise, Lhx5-deficient mice had normal levels of PPI compared to their wild-type controls. These findings, together with those from the Lis1-deficient mice indicate that mice do not need to have normal hippocampal development to display normal sensorimotor gating.

Mouse models of human diseases

Although genetic linkage studies have mapped several different chromosomal regions for schizophrenia, there is still no gene or genes that have been confirmed as

'schizophrenia genes'. Therefore, it has been impossible to evaluate PPI in a mutant mouse created with a mutation in a gene known to cause schizophrenia. However, several mutant lines have been tested that are models of human genetic diseases that either have been shown to have abnormal PPI, or disorders that have aspects of the schizophrenic symptomatology.

Huntington's disease Swerdlow *et al*[8] demonstrated that individuals with Huntington's disease display reduced sensorimotor gating as measured by PPI. Huntington's disease is a progressive neurodegenerative disorder caused by a CAG repeat expansion in the coding region of the huntingtin gene, HD. It has been speculated that the impaired PPI response in Huntington's disease patients reflects abnormal gating of rapidly incoming signals. Several transgenic mouse lines have been created that contain different types of genetic mutations in an attempt to generate a mouse model of Huntington's disease. One of these transgenic mouse lines, known as R6/2, contains exon 1 of the human HD gene carrying 141–157 CAG repeats.[81] These mice display abnormal motor skills and become progressively more hypoactive with aging. The R6/2 transgenic line was also found to have significantly lower levels of PPI than the control mice.[81] Interestingly, deficits in PPI were observed earlier in the lifetime of these mice than were most other phenotypic differences. These findings support the hypothesis that mutations similar to those seen in humans with HD can lead to abnormal sensorimotor gating.

DiGeorge/Velocardiofacial syndrome DiGeorge syndrome/ Velocardiofacial syndrome is the most common form of a disease caused by chromosomal deletion. Individuals with DiGeorge syndrome have a heterozygous deletion of chromosome 22q11.2. DiGeorge syndrome is characterized by craniofacial abnormalities, cardiac dysfunction, and mental retardation. Interestingly, many individuals with DiGeorge display psychotic symptoms reminiscent of the psychosis seen in patients with schizophrenia.[82,83] Although patients with DiGeorge are not schizophrenic, the fact that they display psychotic episodes is quite intriguing and may suggest that there is a gene or genes in the chromosomal region deleted in DiGeorge patients that might lead to increased susceptibility to schizophrenia. There are several lines of mice with mutations in a syntenic region on mouse chromosome 16 that have been used to determine if different genes in this critical region contribute to the pathology that underlies this syndrome.

Single gene mutations in DiGeorge syntenic region To date there have been two reports that studied behavioral responses, including PPI, of mice with single gene mutations in the region of chromosome 16 that is syntenic to the human 22q11. Although individuals with DiGeorge syndrome have heterozygous deletions, information from such single gene mutations could be informative. Female, but not male, mice deficient in catechol-O-methyltransferase (COMT) have altered exploratory activity in a light-dark test of anxiety-related responses. In contrast, male COMT-deficient mice display aggressive behaviors.[84] However, neither male nor female COMT-deficient mice display abnormal PPI,[84] suggesting that this gene does not regulate sensorimotor gating and may not contribute to the 'schizophrenia-like' response of individuals with DiGeorge syndrome.

The Pro/Re hyperprolinaemic mouse strain has a mutation in the gene that codes for proline dehydrogenase (Prodh). Prodh homozygous mutant mice have increased levels of brain proline. Interestingly, Northern analyses revealed an intact message of Prodh in brains of Prodh mutant mice indicating that the Prodh protein is produced with impaired activity (see Gogos *et al*, 1999).[85] While many behavioral responses of the Prodh mutant mice are normal, PPI is impaired,[85] suggesting that mutations in the Prodh gene can lead to impaired sensorimotor gating. Although it is not obvious why these Prodh homozygous mutant mice have normal levels of Prodh message yet deficiencies in proline dehydrogenase activity, the findings indicate that perhaps some of the 'schizophrenia-like' responses observed in DiGeorge syndrome may be related to abnormalities in Prodh gene function.

Heterozygous deletions in DiGeorge syntenic region To develop a better model for DiGeorge syndrome, investigators have created mutant lines of mice that have chromosomal deletions in the mouse syntenic region for DiGeorge syndrome. Kimber *et al*[86]generated mice with a heterozygous deletion of approximately 150 kb using gene targeting. The behavioral responses of these 150 kb deletion mice were evaluated on a test battery that included PPI. The PPI response of the 150 kb deletion mice was abnormal, but somewhat surprisingly the deletion mice had an increased PPI response.[84] The PPI results from the 150 kb deletion mice indicate that a gene, or genes, in this region contribute to PPI, but in an opposite direction from what might have been predicted *a priori*.

Mice with a larger 1.1 mB heterozygous deletion in the DiGeorge critical region have also been generated (*Df1/+* mutant) using chromosomal engineering.[87] Paylor *et al*[88] have just completed a characterization of several behavioral responses, including PPI, of the *Df1/+* mutant mice and found that the mutant mice have impaired PPI. Compared to the wild-type littermates, *Df1/+* mutant mice had significantly lower levels of PPI, especially at the low prepulse sound levels. These findings suggest that a gene or genes in the Df1 region contribute to normal sensorimotor gating and indicate that the *Df1/+* mutant mice may be useful as an animal model for some of the behavioral abnormalities associated with DiGeorge, including their schizophrenia-like behaviors.

It is important to note that actual hearing levels have not been assessed in the DiGeorge mouse models using auditory brainstem recording, so it may be possible some of the impairments may be related to differences

in hearing. We[86] do not believe that this is a cause for the impairment, but future investigations will be performed to directly assess hearing in the *Df1/+* mice. Thus, when performing studies of PPI, it is important to be cautious of the fact that differences in PPI levels can be related to alterations in hearing.

Mouse models of mental retardation
There are numerous mouse models for different forms of mental retardation that are caused by genetic abnormalities. Recent findings using mouse models for fragile X syndrome indicate that altered sensorimotor gating is present in these types of mouse genetic models.[89] The findings from the fragile X mutant mouse suggest that studying PPI responses in individuals with different forms of mental retardation may provide insight into altered sensorimotor gating function associated with these types of disorders.

Fragile X syndrome Fragile X syndrome (FXS) is the most common form of inherited mental retardation[90,91] FXS is caused by an expanded CGG trinucleotide repeat of the *FMR1* gene.[92,93] The expanded repeat results in abnormal methylation and loss of gene expression which leads to the disease. Mental retardation and developmental delay are the most significant clinical features of FXS. However, individuals with FXS have several other prominent behavioral abnormalities including hyperactivity, increased anxiety, motor difficulties, and autistic-like behaviors.[94] Fmr1 knockout mice have been made using standard homologous recombination procedures.[95] The Fmr1 mutant mice display several behavioral abnormalities including increased activity and alterations on tests of anxiety.[95,96]

Recently, Miller *et al*[97] reported that individuals with FXS have increased sensitivity to sensory stimuli using a galvanic skin response test. Although the present review has primarily focused on the use of PPI to assess sensorimotor gating as it relates to neuropsychiatric abnormalities, PPI may also be a good assay for general sensory responsiveness in mutant mice. Although there is only one publication at the time of this review, several groups have shown that Fmr1 knockout mice have abnormal PPI. Chen and Toth[89] recently showed that *Fmr1* knockout mice have significantly higher levels of PPI compared to wild-type mice. Although it is unclear from the paper by Chen and Toth if the wild-type controls were littermates, it may not matter for this mutation because others have found that *Fmr1* knockout mice have higher levels of PPI. In fact, we have just found the *Fmr1* knockout mice have increased PPI, while mice harboring a human YAC of the Fmr1 gene have impaired PPI (McIwain and Paylor, unpublished observations). These findings suggest that the Fmr1 protein plays a role in regulating sensorimotor function and may underlie the increased sensitivity to sensory stimulation that is found in individuals with FXS. Future studies of the PPI response in individuals with FXS are forthcoming.

New candidate genes
Studying the behavioral responses of mutant mice has proved to be a useful way to identify roles for different genes in various behavioral responses that were previously unknown. This section describes several mutant lines of mice that show abnormal PPI responses, but in the absence of any *a priori* hypothesis.

Dishevelled 1 The wingless/Wnt pathway, first described in Drosophila, is a highly conserved development pathway.[98] Dishevelled is a member of the pathway and is required for wingless signaling. There are three closely related Dishevelled (Dvl) genes in mouse. To better understand the role of Dvl in the mammalian system, a mouse deficient in Dvl1 was created using homologous recombination knockout techniques.[99] Dvl1-deficient mice are healthy and develop normally. Many behavioral responses of the Dvl1-deficient mice are also normal. Unexpectedly, we found that Dvl1 KO mice had significantly lower levels of PPI and altered social interactions.[99] The PPI impairment was observed in two independent cohorts of mice and was present when using either an acoustic or tactile startle stimulus. These findings suggest that the Dvl1 gene plays a role in sensorimotor gating and social behavior, and demonstrate how behavioral studies with mutant mice can provide insight into possible gene function. In addition, the findings with the Dvl1 mutant mice suggest that Dvl genes and other members of the Wnt signaling pathway may be candidates for future investigations to determine if there are abnormalities in humans with neuropsychiatric disorders.

Pharmacology of PPI in mice

The behavioral pharmacology of PPI using mice is not nearly as extensive as that with rats. Geyer *et al*[9] provide a comprehensive review of the pharmacology of PPI in rats, including the specific drug actions for most of the agents listed in this review. Therefore, with exceptions for those agents that have not been tested in rats, description of drug actions are not duplicated in this review for simplicity and brevity. Table 1 lists the findings from the studies published to date that describe the effects of different classes of compounds on PPI in mice. When available, the effects of the drugs on the baseline startle are also provided. Although many of these drug effects on PPI have been found to be dose-dependent, doses are not included to simplify the table. The reader interested in the exact doses should refer to the original publication. Finally, results discussed below are not always immediately followed by a citation because all the citations are provided in the table.

There are several interesting features of the pharmacological findings on PPI in mice. First, most of the pharmacological effects on PPI in mice are similar to those found in rats. For both mice and rats, some of the drugs that affect dopaminergic, serotonergic, and glutamatergic receptor systems alter PPI similarly (see

Table 1 Mouse PPI pharmacology

Drug	*Transmitter system*	*Mechanism of Action*	*Strain*	*PPI effect*	*ASR effect*	*References*
Apomorphine	Dopamine	D1/D2 receptor agonist	C57BL/6N	no effect	no effect	100
			129T2/SvEmsJ	impaired	no effect	
			CD-1	impaired	no effect	104
			ddY mice	impaired	no effect	105
			CD-1	no effect	no effect	106
			CFW	impaired	reduced	
			C57BL/6	impaired	reduced	
			129X1/SvJ	no effect	no effect	
			A/J	no effect	no effect	
d-Amphetamine	Dopamine	indirect agonist	C57BL/6N	trend to impair	reduced	100
			CD-1	impaired	no effect	104
			WT (B6J N5)	impaired	reduced	32
			D2 −/−	no efffect	reduced	
			WT (B6J × 129SvJ)	impaired	reduced	
			D3 −/−	impaired	reduced	
			D4 −/−	impaired	reduced	
			C57BL/6J	impaired	reduced	107
			129S6	impaired	reduced	
			129X1	impaired	no effect	
			CD-1	no efffect	no effect	106
			CFW	impaired	reduced	
			C57BL/6	impaired	no effect	
			129X1/SvJ	impaired	no effect	
			A/J	no efffect	no effect	
Clozapine	Dopamine/ Mixed	D1-4/ 5-HT2/ a1/M1-M4 antagonist	C57BL/6J	increased	no effect	109
			DBA/2J	increased	no effect	
			CD-1	no effect	no effect	104
			C57BL/6J	increased	reduced	54
			129S6/SvEvTac	increased	reduced	
			DBA/2	increased	reduced	
			C57BL/6J	increased	reduced	109
			BALB/cJ	increased	reduced	
			MORO	increased	reduced	
			129/SvEvTac	no effect	reduced	
Haloperidol	Dopamine	DA antagonist	C57BL/6J	increased	increased	108
			DBA/2J	increased	no effect	
			CD-1	no effect	no effect	104
			C57BL/6J	increased	reduced	109
			BALB/cJ	increased	reduced	
			MORO	increased	reduced	
			129/SvEvTac	increased	reduced	
Haloperidol + Apomorphine		DA antagonist + DA agonist	CD-1	reduced apo effect	no effect	104
			ddY mice	reduced apo effect	no effect	105
(+)-3-PPP	Dopamine	D2 agonist & sigma ligand	CD-1	trend to increase	no effect	104
Raclopride	Dopamine	D2 antagonist	C57BL/6J	increased	increased	108
			DBA/2J	increased	no effect	
			WT (C57BL/6)	no effect	no effect	32
			DAT +/−	increased	no effect	
			DAT −/−	increased	no effect	
SCH23390	Dopamine	D1 antagonist	WT	no effect	no effect	32
			DAT +/−	no effect	no effect	
			DAT −/−	no effect	no effect	

(*Continued*)

Table 1 Continued

Drug	*Transmitter system*	*Mechanism of Action*	*Strain*	*PPI effect*	*ASR effect*	*References*
Risperidone	Dopamine/ Serotonin	D2 5-HT2A antagonist	C57BL/6J	increased	no effect	108
			DBA/2J	increased	reduced	
			C57BL/6J	no effect	no effect	54
			129S6/SvEvTac	increased	no effect	
			DBA/2	increased	no effect	
			C57BL/6J	increased	reduced	109
			BALB/cJ	increased	reduced	
			MORO	increased	reduced	
			129/SvEvTac	increased	reduced	
RU24969	Serotonin	5-HT1A/1B agonist	WT (129T2/SvEmsJ)	no effect	reduced	25
			5-HT1B KO	no effect	reduced	
			female 1BWT	impaired	no effect	
			female 1BKO	no effect	no effect	
			male 1BWT	impaired	reduced	
			female 1BKO	no effect	reduced	
			WT (129T2/SvEmsJ)	impaired		29
			5-HT1B KO	no effect		
			C57BL/6J	impaired	no effect	101
			129T2/SvEmsJ	impaired	reduced	
			ICR (CD-1)	impaired	increased	
			WT (129T2/SvEmsJ)	impaired	no effect	27
			5-HT1B KO	no effect	no effect	
			5-HT1AKO	impaired	no effect	
8-OH-DPAT	Serotonin	5-HT1A agonist	WT (129T2/SvEmsJ)	increased	reduced	25
			5-HT1B KO	increased	reduced	
			female 1BWT	increased	reduced	
			female 1BKO	increased	no effect	
			male 1BWT	increased	reduced	
			female 1BKO	increased	increased	
			129T2/SvEmsJ	increased		29
			C57BL/6J	no effect	no effect	101
			129T2/SvEmsJ	increased	no effect	
			ICR (CD-1)	increased	no effect	
			WT (129T2/SvEmsJ)	increased	reduced	27
			5-HT1B KO	increased	no effect	
			5-HT1AKO	no effect	no effect	
Flesinoxan	Serotonin	5-HT1A agonist	129T2/SvEmsJ	increased	no effect	27
WAY 100,635	Serotonin	5-HT1A antagonist	129T2/SvEmsJ	no effect		29
WAY 100,636+ 8-OHDPAT	Serotonin	5-HT1A antagonist + 5-HT1A agonist	129T2/SvEmsJ	blocked 8-OHDPAT		29
Buspirone	Serotonin	5-HT1A partial agonist	C57BL/6J	no effect	reduced	109
GR 127935 + MDMA	Serotonin	5-HT1B/1D antagonist + 5-HT releaser	129T2/SvEmsJ	increased	no effect	28
Anpirtoline	Serotonin	5-HT1B agonist	129T2/SvEmsJ	impaired	no effect	27
			WT (129T2/SvEmsJ)	impaired	no effect	
			5-HT1B KO	no effect	no effect	

(*Continued*)

Table 1 Continued

Drug	*Transmitter system*	*Mechanism of Action*	*Strain*	*PPI effect*	*ASR effect*	*References*
DOM	Serotonin	5-HT2A/2C agonist	C57BL/6J	no effect	no effect	101
			129T2/SvEmsJ	no effect	no effect	
			ICR (CD-1)	no effect	no effect	
MDMA	Serotonin	5-HT releaser	C57BL/6J	impaired	no effect	101
			129T2/SvEmsJ	impaired	reduced	
			ICR (CD-1)	impaired	no effect	
			129P3/J	impaired	reduced	100
			129T2/SvEmsJ	no effect		29
			WT	no effect		
			5-HT1B KO	increased		
			WT (129 Sv)	no effect	no effect	27
			5-HT-1B KO	increased	reduced	
MBDB	Serotonin	5-HT releaser	129T2/SvEmsJ	no effect		29
			WT	no effect		
			5-HT1B KO	increased		
			WT (129 Sv)	no effect	no effect	29
			5-HT-1B KO	no effect	reduced	
α-Ethyl-tryptamine (AET)	Serotonin	5-HT releaser	129T2/SvEmsJ	no effect		29
			WT	no effect		
			5-HT1B KO	increased		
Phencyclidine	Glutamate	non-competitive NMDA antagonist	C57BL/6N	impaired	no effect	100
			CD-1	impaired	increased	104
			NMRI	impaired	no effect	110
I-NAM + Phencyclidine	NO + Glutamate	NO synthase inhibitor + NMDA antagonist	NMRI	blocked PCP effect	no effect	110
Dizocilpine	Glutamate	non-competitive NMDA antagonist	CD-1	impaired	increased	104
			CD-1	impaired	no effect	106
			CFW	impaired	no effect	
			C57BL/6	impaired	no effect	
			129X1/SvJ	impaired	no effect	
			A/J	no efffect	no effect	
Haloperidol + Dizocilpine	DA + Glutamate	DA antagonist + NMDA antagonist	CD-1	impaired	increased	104
Clozapine + Dizocilpine	DA + Glutamate	Monoamine antagonist + NMDA antagonist	CD-1	impaired	increased	104
CGS 19755	Glutamate	competitive NMDA antagonist	ddY mice	impaired	no effect	105
Haloperidol + CGS 19755	DA + Glutamate	DA antagonist + NMDA antagonist	ddY mice	impaired	no effect	105
R-CPP (but not SCPP)	Glutamate	competitive NMDA antagonist	ddY mice	impaired	no effect	105
AR-R17779	Acetylcholine	alpha 7 nAChR agonist	DBA/2	no effect	no effect	54
GTS-21		alpha 7 nAChR agonist	DBA/2	no effect	increased	54
Scopolamine	Acetylcholine	Muscarinic antagonist	C57BL/6J	no effect	no effect	109

(*Continued*)

Table 1 Continued

Drug	*Transmitter system*	*Mechanism of Action*	*Strain*	*PPI effect*	*ASR effect*	*References*
Ivermectin	GABA	stimulates release of GABA	C57BL/6J	impaired	increased	111
Diazepam	GABA	GABA agonist	AKR/J	impaired	no effect	109
			C57BL/6J	increased	reduced	
			BALB/cJ	impaired	reduced	
			MORO	no effect	no effect	
			129/SvEvTac	no effect	reduced	
Murine recombinant IL-2	Interleukin	IL-2	Balb/cJ	no effect		112
Morphine	Opioid	Opiate agonist	C57BL/6J	no effect	no effect	109
Clorgyline	Monaminergic	MAO A inhibitor	C3H	impaired	no effect	113
Atipamezole	Adrenergic	alpha 2 antagonist	alpha 2C overexpress	normalized		114
Dexmedetomidine	Adrenergic	alpha 2 agonist	alpha 2C OE	normalized		114
I-NAME	Nitric Oxide	NO synthase inhibitor	NMRI	no effect	no effect	110

Table 1).[9] For example, agents such as the direct dopamine agonist apomorphine, the indirect dopamine agonist amphetamine, and the NMDA antagonist PCP impair PPI in both rats and mice.[100] Nevertheless, there are notable exceptions. For example, 5-HT2 agonists, such as DOM do not appear to affect PPI in either inbred or outbred mouse strains,[101] although several investigators have shown that such drugs consistently disrupt PPI in rats. More strikingly, the 5-HT1A agonists, 8-OH-DPAT and flesinoxan, clearly impair PPI in rats,[9] but increase PPI in mice. As in rats, the effects of the 5-HT1A agonists are appropriately prevented by pretreatment with selective 5-HT1A antagonists such as WAY-100635. Furthermore, the PPI-increasing effects of 8-OH-DPAT are absent in knockout mice lacking 5-HT1A receptors.[27] Thus, although the effects of 5-HT1A agonists on PPI are diametrically opposite in mice *vs* rats, the effects in both species appear to be receptor-specific.

These species-specific differences in 5-HT1A effects on PPI may also explain the disparity observed in the effects of serotonin releasers on PPI in mice *vs* rats. Although a variety of serotonin releasers, such as MDMA, reliably disrupt PPI in rats,[9] the same drugs have minimal and inconsistent PPI-disruptive effects in mice (Table 1). In 5-HT1B knockout mice, however, serotonin releasers increase PPI, presumably because the released serotonin acts upon 5-HT1A receptors. In the absence of 5-HT1B receptors, where serotonin acts to reduce PPI,[25] the influence of 5-HT1A receptor activation predominates. A similar explanation may be relevant to the observation that the serotonin releaser MDMA increases PPI in humans despite decreasing PPI in rats.[102] In both species, it has been demonstrated that these opposite effects of MDMA on PPI are specifically attributable to the serotonin-releasing action of MDMA. Thus, it has been speculated that humans may be more similar to mice than to rats with regards to the influences of 5-HT1A receptors on PPI.[103]

Second, the effects of the various drugs appear to be strain-dependent. Several of the studies listed in Table 1 evaluated the effects of particular drugs in more than one strain of mouse. Although there is no study published to date that has used a panel of a large number of inbred strains to fully characterize the role of genetic background differences on the effect of any one compound, the data published to date confirm that genetic background can be important in the effects of drugs on PPI in mice, as in rats. For example, Dulawa and Geyer[101] showed that 8-OH-DPAT increased PPI in the inbred 129T2/SvEmsJ strain and the outbred ICR strain, but had no effect in the C57BL/6 inbred strain. Similarly, Olivier *et al*[54] suggest that the DBA/2 strain may be more sensitive to antipsychotic drugs than other inbred strains such as the C57BL/6. The field of pharmacogenetics has shown for many years that the effects of drugs depend on genetic background, and although not many strains are typically utilized, this general principle will certainly apply for identifying and understanding the effects of drugs on PPI.

Another interesting aspect of the mouse PPI pharmacology data is that drugs can readily increase PPI, even in the absence of other agents. In general, drugs that increase PPI in rats are most readily detected when they are used in combination with another manipulation that is known to impair PPI. For example, although there are data indicating that clozapine can increase PPI in rats when administered alone, most of the positive effects for clozapine in rats are obtained when it is administered to rats in which PPI has been impaired.[9] In contrast, it is clear that in several strains of mice, clozapine by itself can increase PPI. Although it is not clear why rats and mice differ with respect to some effects of different drugs, the mouse models may

be more useful compared to rats for detecting PPI-increasing effects of different drugs. Although most of the pharmacological studies published using mice have primarily evaluated the effects of certain compounds in isolation, there are several reports that have tested the ability of one compound to block or attenuate the ability of a second drug to impair PPI. For example, Curzon and Decker[104] and Furuya *et al*[105] showed that haloperidol could attenuate or reverse the PPI impairment produced by treatment with apomorphine. These findings are similar to those seen in rats.

A fourth aspect of the findings, which is consistent with what has been shown in rats, is that the effects of drugs on PPI appear to be dissociable from their effects on baseline startle. As shown in Table 1, the increases in PPI produced by antipsychotic drugs are typically associated with decreases in startle reactivity. Nevertheless, amphetamine also typically decreases startle magnitudes in mice, but this effect is associated with impairments of PPI. In contrast, both the non-competitive NMDA antagonist PCP, and ivermectin, which stimulates release of GABA, increase the baseline startle and reduce PPI. Although one should always be cognizant of the possible confounding effects of a drug on PPI by its effects on startle, such dissociations indicate that there is no consistent relationship between the actions of drugs on startle and PPI.

A final aspect of the data presented in Table 1 is that several gene-targeted mutant mice have helped to identify and elucidate the actions of various drugs on PPI. The best example may be the effects of the 5-HT1A/1B agonist RU24969 and the 5HT-1A agonist on PPI. The findings shown in Table 1 indicate that RU24969 impairs PPI while 8-OH-DPAT increases PPI in different strains of mice. These findings suggest different roles for 5-HT1A and 5-HT1B receptors in regulating sensorimotor gating. Studies combining mutant mice and behavioral pharmacology demonstrate that 5-HT1B receptor activation reduces PPI, while 5-HT1A activation increases PPI. In these studies, PPI was impaired following the administration of RU24969 to wild-type mice or 5-HT1A receptor-deficient mice, but not 5-HT1B-deficient mice. In contrast, 8-OH-DPAT increased PPI in wild-type and 5-HT1B, but not in 5-HT-1A, mutant mice. Such data clearly demonstrate that the combined use of genetic and pharmacological tools in mice should provide important insights into the neurobiological basis of sensorimotor gating.

Conclusions

The use of mice in studies of sensorimotor gating will continue to grow, especially studies directed at understanding the role of genes in regulating PPI. Although there are ongoing efforts to use mice to identify chromosomal regions critical for the regulation of sensorimotor gating, it is likely that most information about the genetic basis for sensorimotor gating will come from studies using mutant mice. Findings from studies over the past 5 years show the utility of using mutant mice to study the biological basis of sensorimotor gating. Mutant mice have been used as tools to test specific hypotheses about the role of particular neurotransmitter systems in sensorimotor gating, and to better define and understand the pharmacology of PPI. In addition, mutant mice that have developmental abnormalities of the hippocampal formation yet normal levels of PPI suggest that the hypotheses for a role of abnormal hippocampal development resulting in poor sensorimotor gating may need to be re-evaluated. Screening the PPI response of mice with gene-targeted mutations could identify new target systems that regulate sensorimotor gating. Finally, genetic mutations in particular human diseases that lead to abnormal sensorimotor gating, as may be the case for Huntington's disease, or that lead to psychotic or psychotic-like symptoms, as in the case of DiGeorge syndrome, can be modeled with gene targeting and chromosomal engineering Although there are limitations to the KO strategy including developmental considerations, possible confines related to background strain, and possible influences of flanking regions around mutant genes, gene targeted mutant mice are providing important insights into the genetic and cellular basis for sensorimotor gating.

The future looks bright for the use of mice in studies of PPI. Evaluating the PPI response in mice derived from large-scale mutagenesis projects using chemical mutagens such as ENU, or from high-throughput gene-targeting projects, will provide the research community with more tools to better understand the neurobiology of PPI and the pathology of diseases that lead to impaired sensorimotor gating.

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